Intra-arterial Chemotherapy for Malignant Tumors of Head and Neck Region Using Three Types of Modified Injection Method

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Summary

Relatively higher infusion rate in the intra-arterial chemotherapy (IA chemotherapy) could induce the higher concentration and the more sufficient distribution of chemotherapeutic agents on tumors. To get the relatively higher infusion rate in IA chemotherapy, we used three types of injection method: high-flow injection, high-dose injection with detoxification and flow-controlled injection method for the treatment of malignant brain tumors, skull base tumors and head and neck tumors.

Between January 1997 and October 2001, twenty-seven patients (mean age 61 y.o.) with supratentorial glioblastoma (4 cases), supratentorial anaplastic astrocytoma (1), CNS lymphoma (2), matastatic skull base tumors (3), and neck tumors (15 squamous cell carcinoma, 1 malignant melanoma and 1 neuroblastoma) received our three types of IA chemotherapy. Sixty-five consecutive procedures were performed. Conventional radiation therapy and/or surgical removal were performed in some of these patients. The median follow-up period was 10 months ranging 2 to 56 months.

Fifteen (55.6%) and 6 (22.2%) of 27 patients achieved complete response (CR) and partial response (PR) respectively after initial treatment [CR+PR: 21 (77.8%)]. All responded patients showed clinical improvement. The response rate declined to 55.6% at the end of follow-up period. Eighteen patients are still alive and 15 of them show no evidence of local recurrence. The median post treatment survival was 12 months. There was no serious complication except transient nausea in 4 of 27 (14%) patients, vertigo and granulocytopenia in 1 each (3%) of 27 patients.

Our modified IA chemotherapy has provided favorable clinical and radiological results without technical difficulties and serious complications.

Introduction

A wide variety of modalities, surgery, radiation therapy and chemotherapy, have been used for the treatment of malignant tumors of head and neck regions including brain tumors. Chemotherapy has recently begun to play an important role in the treatment of these lesions. Intra-arterial administration of chemotherapeutic agents is one of the attractive methods to increase the drug delivery and also to decrease potentially systemic toxicities[8]. However the previous reports of intra-arterial chemotherapy (IA chemotherapy) have not necessarily produced satisfactory clinical results[9,21]. Several investigators have recently con-

templated some clinical trials of IA chemotherapy to improve the effectiveness and to reduce the adverse effects. Takeda et Al[17] reported that higher infusion rate could have an effect not only on the streaming phenomenon which results in the brain toxicities, but also on the increase in the concentration and the sufficient distribution of a drug in tumors. Under these experimental data we used three types of modified injection method: high-flow injection (HFI), high-dose injection with detoxification (HDI) and flow-controlled injection (FCI) method.

In this study the initial and follow-up clinical results of our modified three types of IA chemotherapy were examined in 27 patients with malignant tumors of head and neck region including brain tumors.

Table 1 **Histological classification**

Intracranial	Glioblastoma	4
	Malignant glioma	1
	CNS-malignant lymphoma	2
Extracranial	Squamous cell carcinoma	15
	Neuroblastoma	1
	Malignant melanoma	1
Skull tumor	Metastatic tumor	3
	Total	*27*

Table 2 **Initial and final response of all cases (n = 27)**

	Initial response	**Final response**
Complete response	15	11
Partial response	6	4
Stable Disease	1	0
Progressive Disease	5	3
Death	0	9
CR+PR	21 (77.8%)	15 (55.6%)

Patients and Methods

Between January 1997 and October 2001, twenty-seven patients [9 women, 18 men, mean age 61 (15-81) y.o.] with supratentorial glioblastoma (4 cases), supratentorial anaplastic astrocytoma (1), CNS lymphoma (2), matastatic skull base tumors (3), and neck tumors (15 squamous cell carcinoma, 1 malignant melanoma and 1 neuroblastoma) received our three types of injection method of IA chemotherapy (table 1). Sixty-five consecutive procedures were performed. Nine of 27 patients had experienced recurrence.

We used three types of modified IA chemotherapy: high-flow injection (HFI), high-dose injection with detoxification (HDI), and flow-controlled injection (FCI) method as an IA chemotherapy. Injection method in each patient was selected depend on the location of tumors, histological diagnosis and angiographical feeding patterns.

High-flow injection (HFI) was indicated in 7 patients with intra-cranial malignant tumor. Selective intra-carotid cannulation was performed via the femoral artery. The tip of a microcatheter was placed at the supraophthalmic portion of internal carotid artery. Nimustine hydrochloride (ACNU) at a dose of 50-100 mg [Ranimustine (MCNU) 25-80 mg/m^2] diluted to the concentration of 50 mg/20 ml normal saline was prepared. After test injection the chemotherapeutic agent was injected at the flow rate of 20-30 ml/min by a pressure injector. HFI was repeated 2-6 times as maintenance therapy in 6 of 7 patients. Another patient underwent the procedure only once.

High-dose injection with detoxification (HDI) was indicated in 16 patients with extracranial tumor of oro-rhino-pharyngeal region. Selective external carotid artery cannulation was performed by transfemoral approach. The tip of a microcatheter was advanced into the external carotid branch regarded as proper feeding artery. CDDP (solution of 0.5 mg/ml) at a dose of 75-200 mg/m^2 was administered by an infusion pump. To reduce the systemic adverse effect of the chemotherapeutic agent, sodium thiosulfate (STS) at a dose of 100 mg per 1 mg-CDDP was administered into ipsilateral anominate vein through another catheter cannulated via the femoral vein. The rate of infusion was 10 ml/min through the feeding artery and 5 ml/min through the anominate

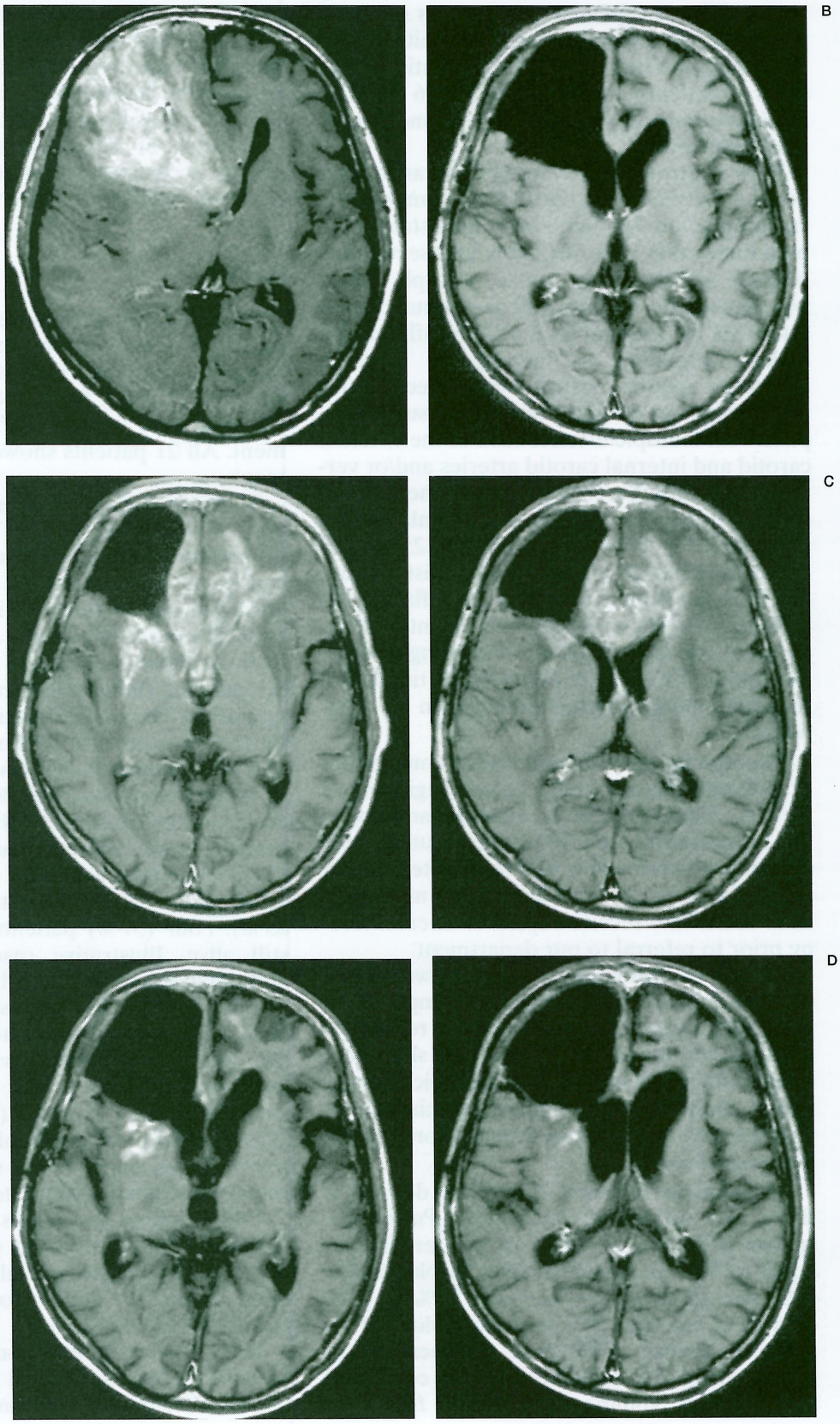

Figure 1 Case 1: High-flow injection. A 47 year-old man with right frontal glioblastoma. A) Preoperative T1-weighted Gd-enhanced image demonstrating a large enhanced mass in right frontal lobe. B) Follow-up MR images obtained one year after the initial treatment (surgical removal and conventional radiation therapy). No evidence of tumor was shown. C) MR images revealing recurrence of tumor obtained 33 months after the initial treatment. D) MR images revealing markedly reducing enhanced lesion and perifocal edema in the bilateral frontal lobes 6 months after the first high-flow intra-arterial injection of ACNU.

vein. HDI was repeated 2-3 times as intensive preoperative chemotherapy concomitant with local radiation therapy in 12 of 16 patients. The other 4 patients underwent HDI 1-6 times as remission-induction or palliative chemotherapy after recurrence.

Flow-controlled injection (FCI) was indicated in 1 patient with maxillary squamous cell carcinoma and 3 patients with metastatic skull base tumor that were surgically unresectable. A balloon catheter with double or triple lumen was placed into the external or internal carotid artery via the femoral artery. After inflating the balloon proximal to the tip of catheter, chemotherapeutic agents were injected. Tumors located in the skull base were usually supplied with multiple arteries such as the external carotid and internal carotid arteries and/or vertebral systems. Accordingly tip of the balloon catheter was placed at the main trunk portion proximal to its branching. CDDP (0.25 mg/ml) at a dose of 60-120 mg/m^2 was administered under flow controlled condition by inflating the balloon. The chemotherapeutic agent was injected at the rate of 200 ml/hour using an infusion pump. FCI was performed 1-4 times as a remission-induction-chemotherapy in all 4 patients.

Twenty-one patients underwent conventional radiation therapy either before beginning of the IA chemotherapy or concomitantly with the IA chemotherapy. Ten patients underwent surgical removal either before or after the IA chemotherapy. One patient with metastatic skull tumor had received systemic chemotherapy prior to referral to our department.

Initial and follow-up evaluation was based on neurological examination and computed tomography scans and/or magnetic resonance imagings in patients with brain and skull base tumor, and it was based on endoscopical observation addition to radiological examination in patients with extra-cranial tumor of oro- rhinopharyngeal region.

A complete response (CR) was defined if there was no tumor recurrence. Partial response (PR) was a reduction greater than or equal to 50% in tumor volume. Stable disease (SD) was an increase of less than 25%, or a reduction of less than 50% in tumor volume. Progressive disease (PD) was an increase of greater than 25% in tumor volume compared with baseline volume. The median follow-up period was 10 months ranging 2 to 56 months.

A statistical analysis of the results was not applicable due to the variety of the disease concerning the histological diagnosis, tumor location as well as the small number of patients.

Toxicity of chemotherapeutic agents was graded according to National Cancer Institute common toxicity criteria (NCI-CTC).

Results

Initial and final response to IA chemotherapy of all patients is shown in table 2. Fifteen complete responses (55.6%) and 6 partial responses (22.2%), for a total of 21 responses (77.8%) were observed after initial IA treatment. All 21 patients showed clinical improvement.

The response rate declined to 55.6% at the end of follow-up period. Three patients had progressive disease and nine patients died. The causes of death included local recurrence in eight and aggravation of primary lesion in 1 patient. The other 18 patients are still alive and 15 of them show no evidence of local recurrence. Six patients showed recurrence during follow-up period. The mean duration to recurrence of these 6 patients was 14.8 months. The median post treatment survival was 12 months.

Table 3 shows the details of 7 patients with brain tumors treated by HFI method. Two of 7 patients were recurrent case. In this group, 5 (71%) patients achieved CR and 1 (14%) achieved PR after initial treatment (CR+PR: 85%). Four (57%) patients in this group are still alive. Illustrative case treated by HFI method is shown in figure 1 and 2.

Table 4 shows the details of 16 patients with head and neck tumors treated by HDI method. The lesion of 7 patients was recurrence after previous treatment. In this group, 7 (44%) patients achieved CR and 5 (31%) achieved PR (CR+PR: 75%) after initial treatment. Eleven (69%) of 16 patients are still alive. Figure 3 shows illustrative case treated by HDI method.

Table 5 shows the details of 4 patients treated by FCI method. In this group, 3 (75%) patients achieved CR and all of them are still alive. Figure 4 and 5 show illustrative case treated by FCI method.

There was no serious complication associated with the angiographical procedures and no failure to cannulate into target vessels. Toxici-

Table 3 **Patients treated by high-flow injection method (n = 7)**

Case	Histology	Adjuvant	Agent	Session	Initial Response	DR(M)	Survival (M)
1) 47 M	GB*	STR, RT	ACNU, MCNU	6	CR	20	56
2) 56 M	ML	STR, RT	MCNU	3	CR	32	36
3) 70 M	MG 3	STR, RT	ACNU	2	CR	NR	50, alive
4) 50 F	GB*	STR, RT	ACNU	3	PR	15	18
5) 76 M	GB	Biopsy, RT	ACNU	1	PD	-	7, alive
6) 77 F	GB	STR, RT	ACNU	2	CR	NR	10, alive
7) 67 F	ML	STR,RT,SC	ACNU	2	CR	NR	2, alive

*GB: glioblastoma, *: recurrence, ML: malignant lymphoma, MG3: malignant astrocytoma grade 3, STR: subtotal removal, RT: radiation therapy, DR: duration to recurrence, NR: no recurrence.*

Table 4 **Patients treated by high-dose injection method (n = 16)**

Case	Histology	Adjuvant	Agent	Session	Initial Response	DR(M)	Survival (M)
1) 48 M	maxilla SCC*	STR, RT	CDDP	2	PD	-	6
2) 73 F	tongue SCC	RT,TR	CDDP	3	CR	NR	15, alive
3) 54 M	epipha.SCC	biopsy, RT	CDDP	2	CR	NR	26, alive
4) 71 F	maxilla SCC	RT,TR	CDDP	2	CR	NR	12, alive
5) 73 M	midpha.SCC*	RT	CDDP	2	PD	-	15
6) 55 M	oral SCC*	TR,RT	CDDP	6	PR	12	12, alive
7) 72 M	midpha.SCC	RT	CDDP	2	CR	12	12, alive
8) 81 F	olf.NB*	RT, EMB	CDDP	1	PR	5	6
9) 65 M	epipha.SCC	RT,TR	CDDP	2	CR	8	8, alive
10) 67 F	tongue SCC	RT	CDDP	1	PD	-	5
11) 49 M	oral mal.mela.*	SCTx	CDDP	3	PR	NR	6, alive
12) 58 M	epipha.SCC*	RT,PR	CDDP	1	PD	-	5
13) 53 M	epipha.SCC	Biopsy, RT	CDDP	1	CR	NR	5, alive
14) 73 M	midpha.SCC*	RT,PR	CDDP	3	PR	NR	1, alive
15) 15 M	epipha.SCC	RT	CDDP	3	PR	NR	1, alive
16) 72 F	tongue SCC	RT,TR	CDDP	2	CR	NR	2, alive

*SCC: squamous cell carcinoma, *: recurrence, STR: subtotal removal, RT: radiation therapy, EMB: embolization SCTx: systemic chemotherapy, DR: duration to recurrence, NR: no recurrence.*

ties included transient nausea in 4 (14%) patients and vertigo in 1 (3%) that resolved in a few day with the use of 5-HT3 antagonist and drip infusion. One patient needed administration of G-CSF because of severe granulocytopenia that returned to baseline within 2 weeks (NCI-CTC grade 2). No neurological toxicity such as seizure, blurred vision and confusion was observed.

Discussion

There have been multiple modalities including surgical removal, radiation therapy and chemotherapy, alone or in combination, for the treatment of malignant tumors of brain, head and neck region. Although the standard method of treatment has been a combination of surgery and irradiation, chemotherapy has recently begun to play an important role in improvement of treatment outcome [1-6,8-15,17-19]. Many investigators have demonstrated the efficacy and the complication of intra-arterial or intravenous chemotherapy for these lesions. Intra-arterial administration of chemotherapeutic agents is thought to have pharmacokinetic advantages which may potentially increase tumor uptake during the first passage of the drug and decrease systemic toxicities. And then it is thought to be able to improve the efficacy and patient survival compared with intravenous administration. Experimental studies have shown that intra-arterial administration could deliver high intra-tumoral concentration of drugs, reduction in tumor size and improve survival of experimental animals [8]. Despite the theoretical advantages and the experimental results, previous clinical reports of IA chemotherapy have not necessarily been satisfactory [9]. Especially according to the cooperative study in 1992 by Shapiro et Al [21], IA chemotherapy was reported to be not only less effective but also more neurotoxic than intra-venous chemotherapy. One of the reasons for these unsatisfactory clinical results after IA chemotherapy may be the heterogeneous and non-uniform delivery of drugs into tumors due to streaming phenomenon after slow infusion rate [1,15,20]. According to our data, 4 ml/min (Shapiro et Al [21]) and 30 ml/15-20 min (Kochi et Al [9]) were too slow to get the sufficient distribution of chemotherapeutic agents in the tumors. Other reasons may be the limitation of drug delivery due to restricted blood-brain barrier permeability and the lack of good chemotherapeutic agents especially in case of malignant brain tumors. Several clinical trials of IA chemotherapy have been performed to resolve above problems.

Saris et Al [15] recommended the diastole-phased pulsatile infusion to assure uniform drug delivery and to reduce neurotoxicities. Aoki et Al [1] concluded that fast pulsatile infusion was superior to slow continuous infusion. Morikawa et Al [11] and Doolittle et Al [3] reported the effectiveness of combination IA chemotherapy with blood-brain barrier (BBB) disruption for the treatment of malignant brain tumors. Gobin et Al [6] described that spatial dose fractionation according to arterial territory and pulsatile delivery were important to avoid neurotoxic complication during IA chemotherapy. Madajewicz et Al [10] demonstrated the effectiveness of combination IA chemotherapy prior to radiation therapy.

To improve the clinical outcome of patients with malignant tumors of the brain, head and neck region after IA chemotherapy, we used three types of modified IA injection: high-flow injection (HFI), high-dose injection with detoxification (HDI), and flow-controlled injection

Table 5 **Patients treated by flow-controlled injection method (n = 4)**

Case	Histology	Adjuvant	Agent	Session	Initial Response	DR(M)	Survival (M)
1) 61 M	SBM(HCC)	Removal	CDDP	4	CR	NR	36, alive
2) 71 M	SBM(PDA)	SCTx	CDDP	1	NC	-	5
3) 53 M	maxilla SCC	biopsy, RT	CDDP	2	CR	NR	12, alive
4) 50 F	SBM(BC)	RT	CDDP	1	CR	NR	24, alive

SBG: skull base metastasis, HCC: hepatocellular carcinoma, PDA: poorly differentiated adenocarcinoma
BC: breast cancer, SCTx: systemic chemotherapy, RT: radiation therapy,DR: duration to recurrence, NR: no recurrence

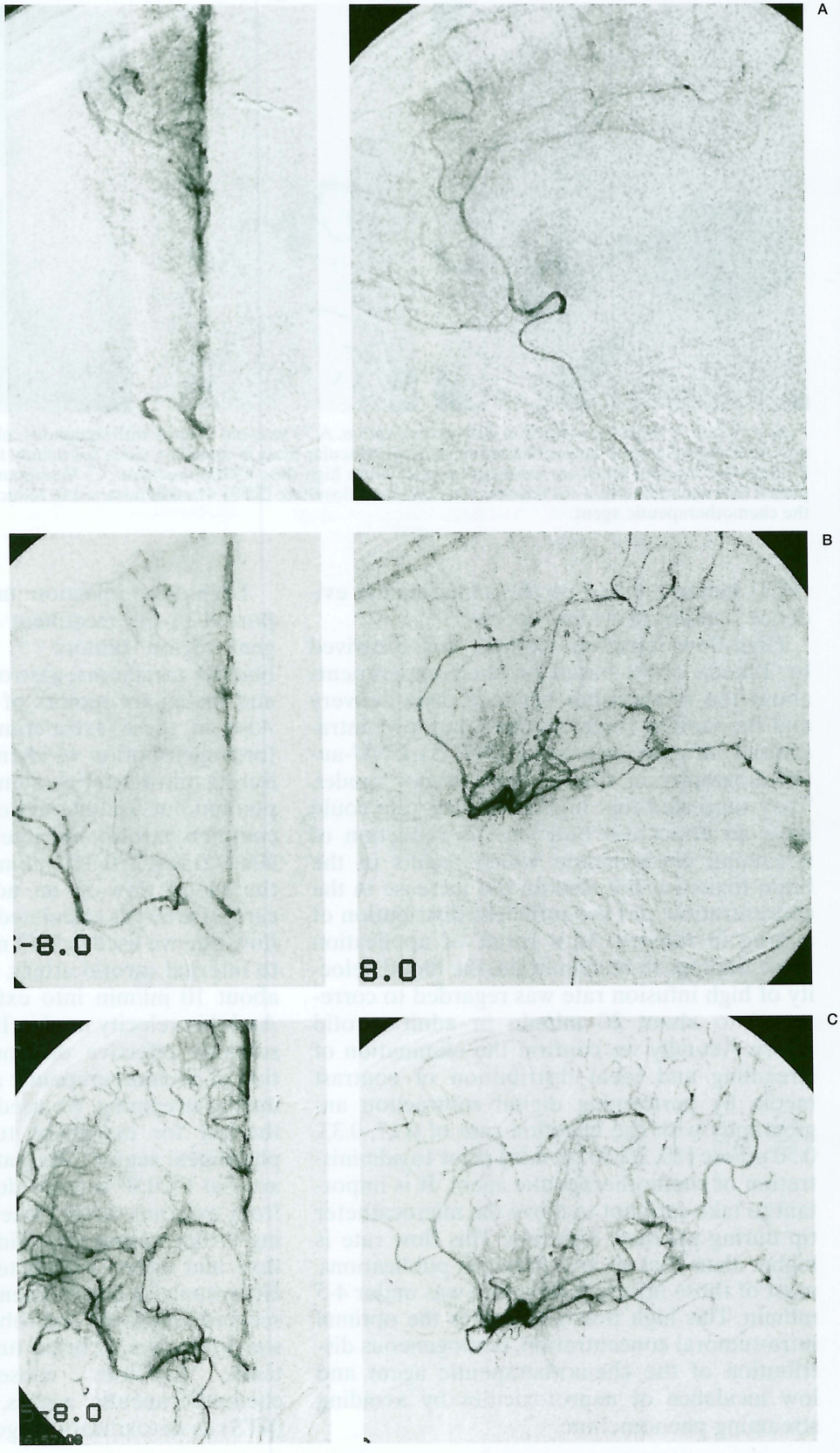

Figure 2 Case 1: High-flow injection. Internal carotid angiogram during three different flow rate injection of contrast medium. Cerebral arteries during low flow rate injection were not filled fully by contrast medium because of streaming phenomenon. A) low flow rate (10ml/min), B) medium flow rate (20ml/min), C) high flow rate (30ml/min).

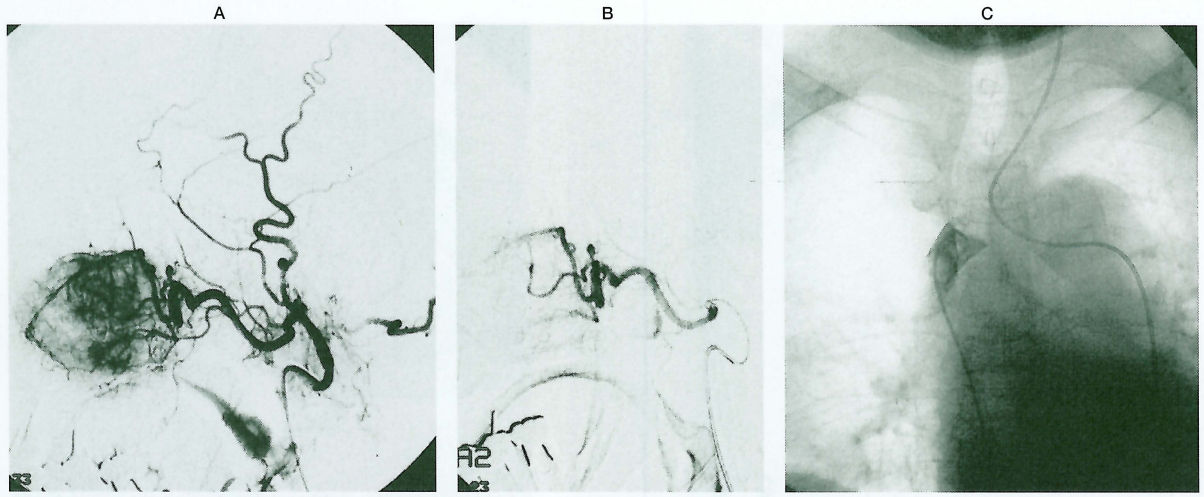

Figure 3 Case 2: High-dose injection with detoxification. A 73 year-old woman with squamous cell carcinoma of maxillary sinus. A) External carotid angiogram revealing hypervascular mass in maxillary sinus fed mainly by internal maxillary artery. B) Selective internal maxillary arteriogram just before high-dose CDDP injection. C) Venogram showing another catheter placed into anominate vein via femoral vein. Sodium thiosulfate (STS) was administered to reduce systemic adverse effect of the chemotherapeutic agent.

(FCI) method, based on the experimental evidence [17] and/or previous reports [7,13,14,16].

High-flow injection method was contrived by Takeda et Al based on their experiments about the relationship between drug delivery and the various (high, medium and low) intra-arterial infusion rate using [3H] SarCNU-autoradiography in C6 rat brain tumor model. They suggested that higher infusion rate could have an effect not only on the reduction of streaming phenomenon which results in the brain toxicities, but also on the increase in the concentration and the sufficient distribution of a drug in tumors. As a result of application these findings to human brain, the blood velocity of high infusion rate was regarded to correspond to about 20 ml/min in adult carotid artery. Actually we confirm the elimination of streaming and ideal distribution of contrast media by performing digital subtraction angiography with the injection rate of 0.17, 0.33, 0.50 ml/sec (10, 20, 30 ml/min) prior to administration of chemotherapeutic agent. It is important to take care not to move the microcatheter tip during pressure injection. This flow rate is higher than that of any previous publications, most of those injection flow rate was under 4-5 ml/min. This high flow rate serves the optimal intra-tumoral concentration, homogeneous distribution of the chemotherapeutic agent and low incidence of neurotoxicities by avoiding streaming phenomenon.

High-dose injection method has been reported in the treatment of oro-rhino-pharyngeal region tumors [13,14], uterine carcinoma [7], bladder carcinoma, gastro-intestinal carcinoma and malignant tumors of orthopedic territory. Also in these extra-cranial tumors, non-uniform distribution of chemotherapeutic agents during intra-arterial administration has been pointed out. The blood flow in an adult human common carotid and internal carotid artery is 400-500 and 270-350 ml/min, respectively. Then the blood flow in an adult human external carotid artery is calculated 130-150 ml/min. The flow rate we used in HFI method, 20 ml/min into internal carotid artery, would correspond to about 10 ml/min into external carotid artery. And this velocity used in HDI method was presumably effective on homogeneous distribution of chemotherapeutic agent in tumor by reducing streaming. We used HDI as an adjuvant therapy for malignant tumors of oro-rhino-pharingeal region. The patients received intra-arterial CDDP as high dose as 75-200 mg/m^2, from external carotid artery branches, increasing or decreasing according to age, renal function and other parameters of each patient. Neurotoxicity due to chemotherapeutic agents seemed relatively unproblematic in comparison with cases of brain tumors. To reduce systemic toxicities caused by high-dose chemotherapeutic agents, sodium thiosulfate (STS) as detoxification agent against CDDP at

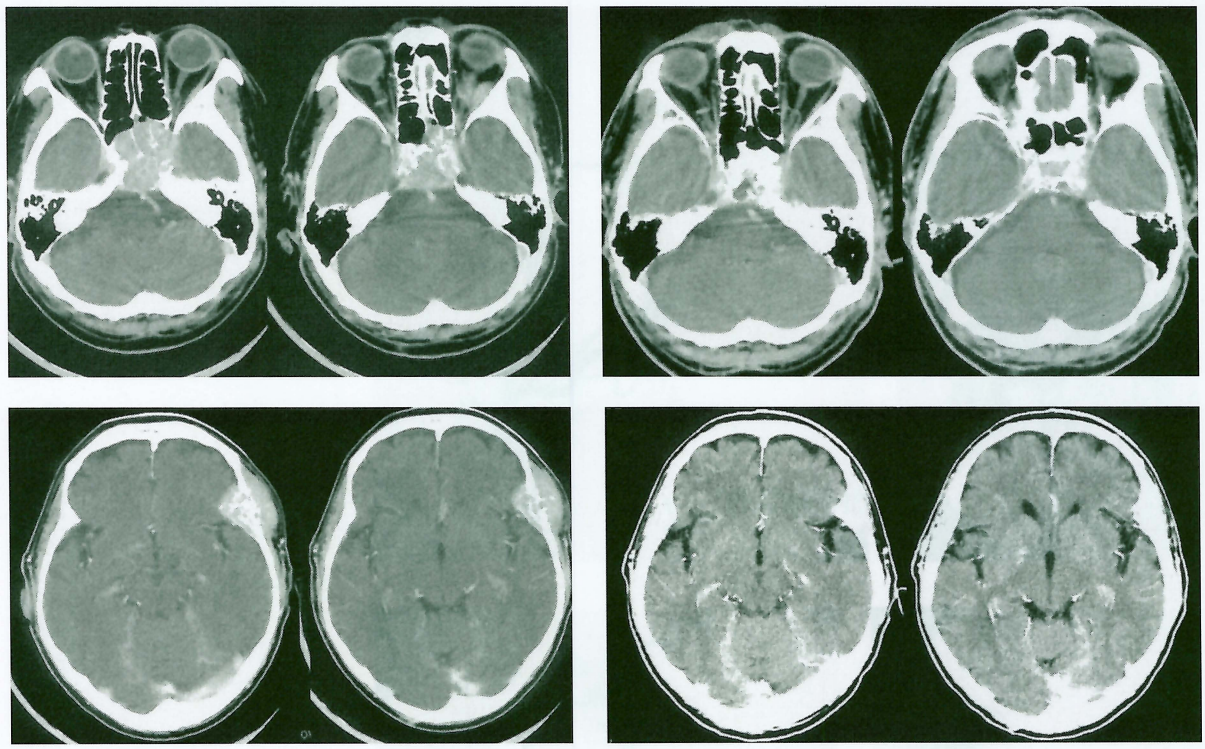

Figure 4 Case 3: Flow-controlled injection. A 61 year-old man with skull base metastasis from hepatocellular carcinoma. A) Initial contrast enhanced CT scans demonstrating enhanced mass lesions involving sphenoid sinus and left temporal bone with bone destruction. B) Contrast enhanced CT scans obtained 1 year after 4 sessions of flow controlled injection of CDDP. No evidence of residual tumor was shown.

a dose of 100 mg per 1mg-CDDP was administered into ipsilateral draining venous system. The combination of detoxification is particularly useful because it enables repeated IA chemotherapy in terms as short as two or three times a month.

There are few previous reports concerning the flow-controlled intra-arterial injection of chemotherapeutic agents. Sawada et Al [16] demonstrated that balloon occluded arterial infusion therapy was effective for the treatment of progressive uterine cervical carcinoma by increasing intratumoral concentration of the drugs. We tried FCI for 3 patients with skull base metastasis and 1 maxillary sinus cancer. In FCI method, the tip of balloon catheter was placed at the main trunk portion proximal to branching. Chemotherapeutic agent was administered under flow-controlled condition by inflating the balloon. Usually in case of skull base tumor, the feeding pattern is complimentary from the external and internal carotid arteries and/or vertebral systems. If tumor was supplied with 1 or 2 proper feeders, HDI was indicated. And if tumor was supplied with multiple feeders from the external and internal carotid arteries and/or vertebral systems, FCI was also indicated. Flow-controlled injection method is based largely on the same theory governing high-flow injection. By reducing the blood flow to tumor after the inflation of balloon proximal to the tumor, the rate of infusion becomes relatively high and streaming phenomenon is consequently reduced, which causes sufficient distribution of a drug in the tumors.

Initial IA chemotherapy trial [21] resulted in unacceptable toxicities. Recently Gelman et Al [5] reported IA chemotherapy-related complications in their series of 48 patients: groin haematoma (2.6%), carotid arterial dissection (0.5%), transient neurological event (1.8%) and transient seizure (1.5%). They concluded IA chemotherapy is a safe procedure with low complication rate. In our series there was no serious complication associated with the angiographical procedures and no failure to cannulate target vessels.

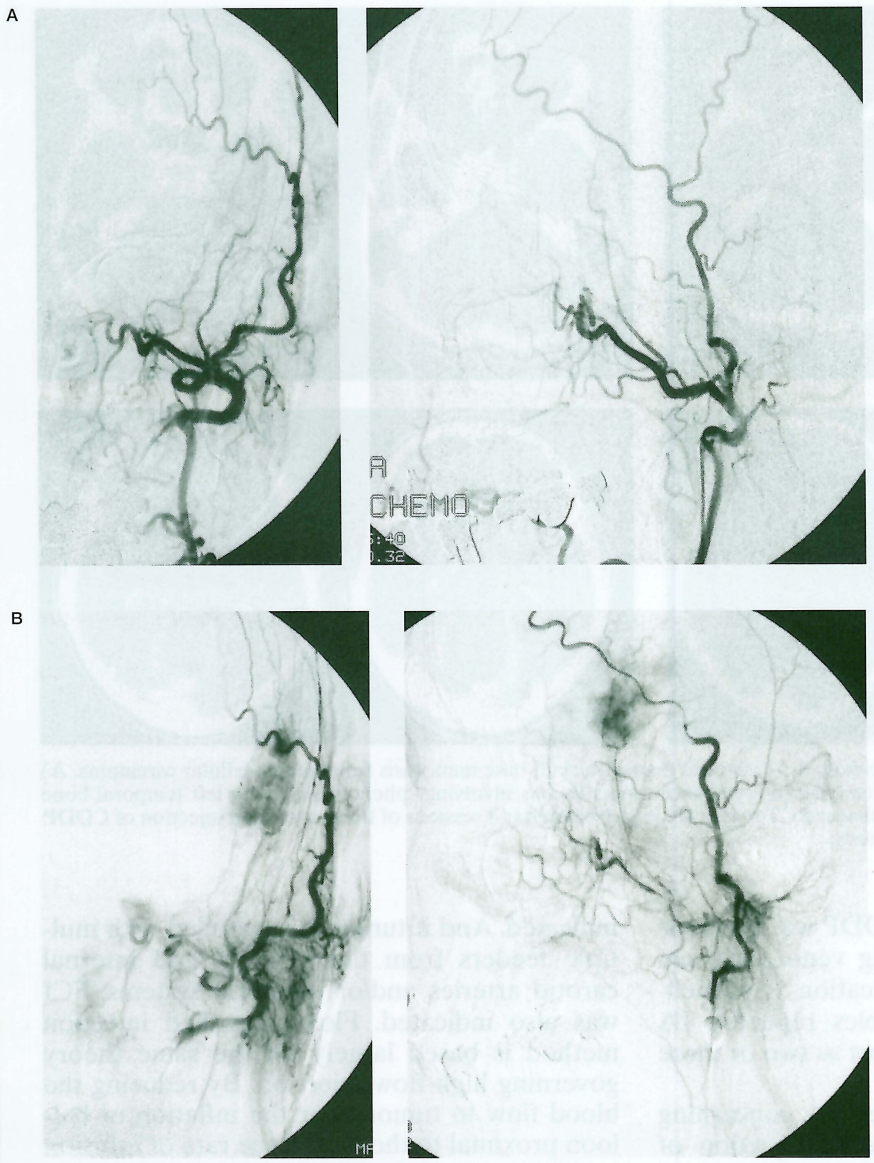

Figure 5 Case 3: Flow-controlled injection. A) Left external carotid angiograms obtained before inflating the balloon. B) Left external carotid angiograms during flow-controlled injection revealing increased concentration of contrast-enhanced material to the tumor.

Gentle maneuver and administration of vasodilator (calcium antagonist) are required not to injure the feeding arteries. Tfayli et Al [19] evaluated for the toxicities of their 168 patients and reported that nausea and vomiting were the most common toxicities (14%), and transient neurologic toxicities were observed in 22 patients (5.6%). In our series transient nausea was observed in 4 (14%), vertigo in 1 (3%), granulocytopenia in 1 (3%) and neurological toxicities in none patients. We think IA chemotherapy is a relatively safe treatment modality.

Of 27 patients who received our modified IA chemotherapy, 17 patients experienced complete response (55.6%) and 6 patients experienced partial response (22.2%) for a total of 21 patients (77.8%) favorably responded to the treatment. Considering that all patients in this series were with high-grade malignant tumor and 9 patients had experienced recurrend this clinical results seemed to be enough acceptable. It is well known that the tumor become resistant to the chemotherapeutic agent which used several times.

In estabilishing the most effective treatment for malignant tumors of the brain, head and neck region, it is crucial to select the most ap-

propriate injection method in regard to the tumor's location, histological diagnosis and angiographical feeding pattern. These criteria should be applied to each patient in order to provide better clinical results accompanied by minimal adverse effects.

Conclusions

Twenty-seven patients with malignant tumors of head and neck region including brain tumors were treated by our modified three types of intra-arterial chemotherapy; high flow injection method (HFI), high dose injection with detoxification method (HDI) and flow controlled injection method (FCI).

These provided favorable clinical and radiological results (initial and final response rate was 77.8% and 55.6% respectively) without technical difficulties and serious complications.

HFI is recommended for patients with intracranial tumors. HDI or FCI should be selected for patients with extra-cranial tumors according to the angiographical findings.

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